A1 CONT. Rule B1

2. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO: 2; and

(b) hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 1 or the complement thereof.

RESPONSE

I. Status of the Claims

Claims 1 and 2 have been amended. No new claims have been added. Claims 1-3 are therefore presently pending in the case. For the convenience of the Examiner and in compliance with 37 C.F.R. § 1.121(c)(1)(ii), a marked up copy of the original claims is attached hereto as **Exhibit A** and a clean copy of the pending claims is attached hereto as **Exhibit B**.

II. Support for the Amended Claim

Claim 1 has been amended to further clarify the claim, and to recite that the isolated nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:1. Support for this claim can be found throughout the specification as originally filed, with particular support being found at least in Claim 1 and SEQ ID NO:1 as originally filed as well as in Section 5.1.

Claim 2 has been amended to further clarify the claim, and to recite highly stringent conditions. Amendment of Claim 2 finds support throughout the specification as originally filed, with particular support and a definition of highly stringent hybridization being found at page 4, lines 16-20.

As the amendments to Claims 1 and 2 are fully supported by the specification and claims as originally filed, they do not constitute new matter. Entry therefore is respectfully requested.

III. Claim Objection

The Action objects to Claim 3 under 37 C.F.R. 1.75 as being a duplicate of Claim 2 part a). Applicants believe and intended that the use of the term "and" in Claim 2 indicates that both the limitation of part (a) and the limitation of part (b) apply. As Applicants intended that both limitations

were encompassed by Claim 2, the scope of Claim 2 and Claim 3 are different and, therefore, the objection should be withdrawn.

IV. Rejection of Claims 1-3 Under 35 U.S.C. § 101

The Action rejects claims 1-3 under 35 U.S.C. § 101, allegedly because the claimed invention lacks support by either a specific and substantial asserted utility or a well established utility. Applicants respectfully traverse.

According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

The biological significance and function of neurolysin and neurolysin like metalloproteases are well known to those of skill in the art, including the authors of the publication cited as being allegedly anticipating prior art in the rejection of Claim 1 under 35 U.S.C. § 102(b)(Kato, *et al.*, J. Biol Chem. 1997, 272, 15313-15322) for their role in intracellular degradation of bioactive oligopeptides.

The Action (at page 4, line 1) states "Until an actual and specific biologic significance can be attributed to the NHP and gene encoding it, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention."

Thus the Action alleges that Applicants have failed to characterize the function and activity of the claimed polypeptide sequences. Applicants respectfully disagree and submit that those skilled in the art would clearly believe that the present invention is indeed a neurolysin. This assertion is strongly supported by, among others, GENBANK Accession No. AJ300837 that describes a sequences annotated by others to be the mRNA for human neurolysin that has a 99% identify with the nucleic acid sequence of SEQ ID NO: 1 (2113 of a total of 2115 bases present in SEQ ID NO: 1). These sequences have been defined by third party scientists, wholly unaffiliated with Applicants, as encoding human neurolysin. Given this clear evidence that those skilled in the art have independently accepted the utility described in the present specification, there can be no question that Applicants' asserted utility for the described sequences is "credible." As such, the scientific evidence of record clearly establishes

that Applicants have described a utility in full compliance with the provisions of 35 U.S.C. section 101, and the Examiner's rejection should be withdrawn.

Although the above discussion is believed to be dispositive of the utility issue, the Applicants would like to further direct the Examiner's attention to the parts of the specification (Sections 5.0 and 5.1) that describe the use of sequences in a gene chip format to provide a high throughput analysis of the relevant cellular "transcriptome".

Evidence of the "real world" substantial utility of the present invention is provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, two such companies (Agilent acquired by American Home Products and Rosetta acquired by Merck) were viewed to have such "real world" value that they were acquired by large pharmaceutical companies for significant sums of money. The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. The sequences of the present invention describe a novel gene encoding a neurolysin and provide a unique identifier of the corresponding gene. Such gene chips clearly have utility, as evidenced by the multitude of issued U.S. Patents, such as U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776 to name but a few. The present nucleotide sequences clearly encode a novel human neurolysin as is detailed throughout the specification. Therefore, since the present sequences are specific markers of the human genome, and given that such specific markers define the targets for the discovery of drugs that are associated with human disease, those skilled in the art would clearly recognize that the present nucleotide sequences describe a novel and ideal resource for assessing gene expression using gene chip-related methodologies.

The Examiner is further requested to consider that, given the huge expense of the drug discovery process, even negative information has great "real world" practical utility. Knowing that a given gene is not expressed in medically relevant tissue provides an informative finding of great value to industry by allowing for the more efficient deployment of expensive drug discovery resources. Such practical considerations are equally applicable to the scientific community in general, in the time and resources that are not wasted chasing what are essentially scientific dead-ends (from the perspective

of medical relevance). Clearly, compositions that enhance the utility of such gene chips, such as the presently claimed nucleotide sequences, must in themselves be useful. Moreover, the presently described novel neurolysin provides uniquely specific sequence resources for identifying and quantifying full length transcripts that were encoded by the corresponding human genomic locus. Accordingly, there can be no question that the described sequences provide an exquisitely specific utility for analyzing gene expression.

Yet another example of the utility of the present invention is in expanding the utility of data coming from the human genome project. Persons of skill in the art, as well as thousands of venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. All current therapeutics directly or indirectly interact with biological sequences encoded by the human genome, and virtually all future human therapeutics shall do likewise. Consequently, billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304). The results have been a stunning success, as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, Science *291*:1153). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years).

Although Applicants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (C.C.P.A. 1964); *In re Malachowski*, 189 USPQ 432 (C.C.P.A. 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), as a further example of the utility of the presently claimed polynucleotides, the Examiner is respectfully reminded that only a minor percentage of the genome actually encodes exons that in-turn encode polypeptide sequences. The presently described cDNAs provide biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the described cDNA sequences define which exons are actually spliced together to produce an active transcript (*i.e.*, such sequences are generally required to conclusively identify functional exon splice-junctions). The

Applicants submit that one skilled in the art would have clearly understood that the above *substantial and specific* utilities as inherent features of the presently described sequences.

For the many convincing reasons described above, the present invention clearly has specific, substantial, credible and well established utility. Therefore, Applicants submit that the rejection of Claims 1-3 under 35 U.S.C. § 101 has been overcome and the Examiner is respectfully requested to withdraw the pending rejection of Claims 1-3 under 35 U.S.C. § 101.

V. Rejection of Claims 1-3 Under 35 U.S.C. § 112, First Paragraph

The Action rejects claims 1-3 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the claimed invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully disagree.

Applicants submit that as claims 1-3 have been shown to have a specific, substantial, credible and well established utility, as detailed in section IV, above. Applicants therefore respectfully request that the rejection of claims 1-3 under 35 U.S.C. § 112, first paragraph, be withdrawn.

VI. Rejection of Claim 2 Under 35 U.S.C. § 112, Second Paragraph

The Action rejects claim 2 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the invention. Claim 2 stands rejected because the phrase "stringent conditions" is alleged to be indefinite. Although Applicants believe that this claim as originally filed sufficiently points out and distinctly claims the invention, in order to more rapidly progress the case to allowance, Applicants have amended Claim 2 to specify "highly" stringent conditions. Highly stringent conditions for full length molecules are defined in the specification on page 4, lines 16-20. Applicants, therefore, respectfully submit that this rejection has been avoided by Applicant's amendment of Claim 2 to specify "highly" stringent conditions. Accordingly, the Examiner is respectfully requested to withdraw the pending rejection of Claim 2 under 35 U.S.C. § 112, second paragraph.

VII. Rejection of Claim 1 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects Claim 1 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse.

35 U.S.C. § 112, first paragraph, requires that the specification contain a written description of the invention. The Federal Circuit in *Vas-Cath Inc. v. Mahurkar* (19 USPQ2d 1111 (Fed. Cir. 1991); "*Vas-Cath*") held that an "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.*" *Vas-Cath*, at 1117, emphasis in original. However, it is important to note that the above finding uses the terms reasonable clarity to those skilled in the art. Further, the Federal Circuit in *In re Gosteli* (10 USPQ2d 1614 (Fed. Cir. 1989); "*Gosteli*") held:

> Although [the applicant] does not have to describe exactly the subject matter claimed, . . . the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.

Gosteli at 1618, emphasis added. Additionally, *Utter v. Hiraga* (6 USPQ2d 1709 (Fed. Cir. 1988); "*Utter*"), held "(a) specification may, within the meaning of 35 U.S.C. § 112 ¶1, contain a written description of a broadly claimed invention without describing all species that claim encompasses" (*Utter*, at 1714). Therefore, all Applicants must do to comply with 35 U.S.C. § 112, first paragraph, is to convey the invention with reasonable clarity to the skilled artisan.

Further, the Federal Circuit has held that an adequate description of a chemical genus "requires a precise definition, such as by structure, formula, chemical name or physical properties" sufficient to distinguish the genus from other materials. *Fiers v. Sugano*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993; "*Fiers*"). *Fiers* goes on to hold that the "application satisfies the written description requirement since it sets forth the . . . nucleotide sequence" (*Fiers* at 1607). In other words, provision of a structure and formula - the nucleotide sequence - renders the application in compliance with 35 U.S.C. § 112, first paragraph.

More recently, the standard for complying with the written description requirement in claims involving chemical materials has been explicitly set forth by the Federal Circuit:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. *Univ. of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Thus, a claim describing a genus of nucleic acids by structure, formula, chemical name or physical properties sufficient to allow one of ordinary skill in the art to distinguish the genus from other materials meets the written description requirement of 35 U.S.C. § 112, first paragraph. As further elaborated by the Federal Circuit in *Univ. of California v. Eli Lilly and Co.*:

> In claims to genetic material ... a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA', without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art cannot, as one can do with a fully described genus, visualize or recognize the identity of members of the genus. (Emphasis added)

Thus, as opposed to the situation set forth in *Univ. of California v. Eli Lilly and Co.* and *Fiers*, the nucleic acid sequences of the present invention are not distinguished on the basis of function, or a method of isolation, but in fact are distinguished by structural features - a chemical formula, *i.e.*, the *sequence itself.*

Using the nucleic acid sequences of the present invention (as set forth in the Sequence Listing), the skilled artisan would readily be able to distinguish the claimed nucleic acids from other materials on the basis of the specific structural description provided. Polynucleotides comprising the nucleotide sequence of SEQ ID NO:1, or a nucleotide sequence that encodes SEQ ID NO:2, are within the genus of the instant claims, while those that lack this structural feature lie outside the genus. Claim 1 thus meets the written description requirement.

For each of the foregoing reasons, Applicants submit that the rejection of Claim 1 under 35 U.S.C. § 112, first paragraph, due to lack of written description has been overcome, and request that the rejection be withdrawn.

The Action also rejects claim 1 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants respectfully disagree with the present rejection. Applicants position is that the response provided for the rejection of Claim 1, regarding its alleged lack of written description, clearly demonstrates that the specification contains sufficient written description to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. Therefore, as the Action states (page 6, line 12) that "Due to lack of written description, see above rejection, no one skilled in the art is able to construct the claimed DNA molecule comprising any of 24 contiguous base fragment of SEQ ID NO:1" and thus as written description requirement has been meet, it follows that one skilled in the art would also be able to make and/or use the claimed invention. Claim 1 thus meets the enablement requirement.

However, as Claim 1 has been amended to recite the full length of the nucleotide sequence of SEQ ID NO:1, Applicants submit that the rejection of Claim 1 under 35 U.S.C. § 112, first paragraph has been thus avoided and respectfully request withdrawal of the pending rejection of Claim 1 under 35 U.S.C. § 112,first paragraph.

VIII. Rejection of Claim 1(3) Under 35 U.S.C. § 102(b)

The Action rejects Claim 3 under 35 U.S.C. § 102(b), as being allegedly anticipated by Kato, *et al.*, (J. Biol Chem. 1997, 272, 15313-15322). The Action states (page 8, line 4), that the claim is directed to an isolated DNA molecule comprising at least 24 contiguous bases of nucleotide sequence disclosed in SEQ ID NO:1.

The Examiner's statement does not make sense unless one assumes that it was meant to be applied to Claim 1 (which recited the limitation at issue) and, therefore, it is Applicants belief that the Examiner intended to reject Claim 1 under 35 U.S.C. § 102(b) rather than Claim 3. If the previous discussion provides an accurate portrayal of the Examiner's intended position, Claim 1 presumably stands rejected under 35 U.S.C. § 102(b), as allegedly anticipated by Kato, *et al.*, (J. Biol Chem. 1997, 272, 15313-15322). While Applicants do not necessarily agree with the present rejection, given that Claim 1 has been amended to recite the full length of the nucleotide sequence of SEQ ID NO:1, Applicants submit that the presumed rejection of Claim 1 under 35 U.S.C. § 102(b) has been thus avoided by amendment.

IX. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Walicka have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

This response is timely filed and Applicants believe no fees are due in connection with this response. However, should this be incorrect the Commissioner is authorized to charge any required fees or credit any overpayment to Deposit Account No. 50-0892.

Respectfully submitted,

April 18, 2002
Date

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Exhibit A

Marked-up Version of The Pending Claims in U.S. Patent Application Ser. No. 09/833,782

1. 1. (Amended) An isolated nucleic acid molecule comprising [at least 24 contiguous bases of] the nucleotide sequence [first disclosed in] of SEQ ID NO:1.

2. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO:2; and

(b) hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO:1 or the complement thereof.

3. An isolated nucleic acid molecule comprising a nucleotide sequence encoding the amino acid sequence shown in SEQ ID NO:2.